Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of the Claims:

Claims 1-6 (canceled).

Claim 7 (currently amended): An assay for selecting a compound useful for treating epilepsy or other neurological disorders ~~which modulates inactivation of~~ associated with an abnormal activity of a voltage gated sodium channel, wherein said compound reduces human SCN1A sodium channel activity, said assay comprising:

a) an SCN1A nucleic acid sequence which encodes ~~an~~ human SCN1A sodium channel ~~or a functional fragment thereof~~; and

b) assaying an SCN1A ion channel activity ~~function of said sodium channel~~;

wherein said compound is selected when a ~~difference~~ reduction is observed between ~~the inactivation of~~ said SCN1A sodium channel activity in the presence of a test ~~agent~~ compound, as compared to in the absence thereof.

Claim 8 (currently amended): An assay for selecting, a compound ~~useful for treating epilepsy or other neurological disorders~~ which ~~modulates~~ reduces the activity of a human SCN1A sodium channel comprising:

a) an SCN1A nucleic acid sequence which encodes ~~an~~ human SCN1A sodium channel ~~or functional fragment thereof~~; and

b) assaying an activity of said SCN1A sodium channel;

wherein a compound is selected when a ~~difference~~ reduction is observed between the activity of said SCN1A sodium channel in the presence of ~~said~~ a test ~~agent~~ compound, as compared to in the absence thereof.

Claim 9 (cancelled).

Claim 10 (currently amended): ~~A method~~An assay for identifying, from a library of test compounds, ~~a compound having a therapeutic effect on epilepsy or other neurological disorders~~a compound which reduces a human SCN1A ion channel activity comprising:

a) providing a screening assay which ~~comprises~~ assesses a measurable SCN1A biological activity;

b) contacting said screening assay with a test compound; and

c) detecting if said test compound modulates said SCN1A biological activity;

wherein a ~~test~~ compound ~~which modulates said biological activity~~ is identified ~~as a compound with said therapeutic effect~~ when a reduction is observed between a biological activity of said SCN1A in the presence of said compound, as compared to in the absence thereof.

Claims 11-13 (canceled).

Claim 14 (currently amended): The ~~method~~ assay of claim 10, wherein said SCN1A biological activity in step a) is provided by ~~assay comprises~~ an expression vector comprising a~~n~~ human SCN1A nucleic acid sequence which encodes said SCN1A sodium channel ~~or functional fragment thereof~~.

Claims 15-19 (cancelled).

Claim 20 (currently amended): The ~~method~~ assay of claim ~~19~~14, wherein said SCN1A nucleic acid sequence is ~~a human sequence which comprises a sequence~~ selected from ~~among~~ the group consisting of SEQ ID NOs: 189-192, or an allelic variant thereof.

Claim 21 (currently amended): The ~~method~~ assay of claim 20, wherein said SCN1A nucleic acid sequence ~~is~~ comprises a sequence selected from ~~among the sequences as set forth in~~ the group consisting of SEQ ID NOs:1-2 and 5-32, or an allelic variant thereof.

Claim 22 (currently amended): The ~~method~~ assay of claim 8, wherein said SCN1A nucleic acid sequence encodes the amino acid sequence as set forth in SEQ ID NO:3 or SEQ ID NO: ~~4, or a fragment thereof~~.

Claim 23 (currently amended): The ~~method~~ assay of claim 20, wherein said SCN1A nucleic acid sequence identity has greater than 95% sequence identity thereto.

Claim 24 (currently amended): The ~~method~~ assay of claim 8, wherein said assaying is performed in a cell-free system.

Claim 25 (currently amended): The ~~method~~ assay of claim 8, wherein said assaying is performed with a whole cell.

Claim 26 (currently amended): The ~~method~~ assay of claim 10, wherein said screening assay is a cell-free system.

Claim 27 (currently amended): The ~~method~~ assay of claim 10, wherein said screening assay is a whole cell system.

Claim 28 (currently amended): The ~~method~~ assay of claim 8, wherein said SCN1A nucleic acid sequence is comprised in an expression vector.

Claim 29 (currently amended): The ~~method~~ assay of claim 28, wherein said expression vector is comprised in a cell.

Claim 30 (currently amended): The ~~method~~ assay of claim 8, wherein said SCN1A sequence is a recombinant form of SCN1A.

Claim 31 (new): An assay for selecting a compound for treating epilepsy or other neurological disorders associated with an abnormal activity of a voltage gated sodium channel, wherein said compound reduces SCN1A sodium flux activity, said assay comprising:

a) a SCN1A nucleic acid sequence which encodes a human SCN1A sodium channel; and

b) assaying SCN1A-dependent sodium flux activity;

wherein said compound is selected when a reduction is observed between the SCN1A sodium flux in the presence of a test compound, as compared to in the absence thereof.

Claim 32 (new): An assay for selecting a compound which reduces the activity of a SCN1A sodium channel comprising:

a) a SCN1A nucleic acid sequence which encodes a human SCN1A sodium channel; and

b) assaying SCN1A-dependent sodium flux channel activity;

wherein a compound is selected when a reduction is observed between the sodium flux channel activity of said SCN1A in the presence of a test compound, as compared to in the absence thereof.

Claim 33 (new): An assay for selecting a compound useful for treating epilepsy or other neurological disorders associated with an abnormal activity of a voltage gated sodium channel, wherein said compound reduces human SCN1A sodium channel activity, said assay comprising:

(a) a SCN1A nucleic acid sequence which encodes a human SCN1A sodium channel; and

(b) assaying a SCN1A ion channel activity by assaying at least one of:

i) voltage dependence activation;

ii) voltage dependence of steady state level of inactivation;

iii) time course of inactivation;

iv) the number or fraction of channels available for opening;

v) change in current;

vi) time course of recovery from inactivation;

vii) flux of ions through the channel;

viii) phosphorylation of channel;

ix) binding of molecules to the channel; and

x) induction of a second cellular messenger,

wherein said compound is selected when a reduction is observed between said SCN1A sodium channel activity in the presence of a test compound, as compared to in the absence thereof.

Claim 34 (new): The assay of claim 7, wherein said SCN1A ion channel activity is assessed by at least one of:

I) voltage dependence activation;

II) voltage dependence of steady state level of inactivation;

III) time course of inactivation;

IV) the number or fraction of channels available for opening;

V) change in current;

VI) time course of recovery from inactivation;

VII) phosphorylation of channel;

VIII) flux of ions through the channel;

IX) binding molecules to the channel; and

X) Induction of a second cellular messenger.

Claim 35 (new): The assay of claim 33, wherein said flux of ions through the channel is assessed by one of the group consisting of:

i) fluorescence resonance energy transfer (FRET)-based voltage sensor assay;

ii) dibasic dyes;

iii) radiolabeled guanindine;

iv) two electrode voltage clamp; and

v) patch-clamp.

Claim 36 (new): The assay of claim 33, wherein said binding of molecule to the channel is assessed by surface plasmon resonance.

Claim 37 (new): The assay of claim 34, wherein said flux of ions through the channel is assessed using one of the group consisting of:

i) fluorescence resonance energy transfer (FRET)-based voltage sensor assay;

ii) dibasic dyes;

iii) radiolabeled guanindine;

iv) two electrode voltage clamp; and

v) patch-clamp.

Claim 38 (new): The assay of claim 34, wherein said binding of molecule to the channel is assessed by surface plasmon resonance.

Claim 39 (new): An assay for selecting a sodium channel blocker useful for treating idiopathic generalized epilepsy (IGE) or other neurological disorders associated with an abnormal activity

of a voltage gated sodium channel, wherein said blocker affects a human SCN1A sodium channel, said assay comprising:

a) a SCN1A nucleic acid sequence which encodes a SCN1A sodium channel; and

b) assaying a SCN1A ion channel activity,

wherein said blocker is selected when a difference is observed between said SCN1A sodium channel activity in the presence of a test compound, as compared to in the absence thereof.

Claim 40 (new): The assay of claim 7, wherein said compound is selected from a library of test compounds.

Claim 41 (new): The assay of claim 8, wherein said compound is selected from a library of test compounds.

A Response to the Office Action Dated September 1, 2004:

A. Comments On the Office Action Dated September 1, 2004

The Office Action dated September 1, 2004 states that Applicants' previous response was not fully responsive to the prior Office Action dated December 22, 2003. Specifically, the Action takes issue with the listing of claims 1-6 and 11-13 as "withdrawn" instead of "canceled."

Applicants note that claims 1-6 and 11-13 are now listed as "canceled." Applicants have also included the text of the response that was filed with the U.S. Patent Office on June 22, 2004 into the present document for the Examiner's convienience. Applicants believe that this document fully responds to the September 1, 2004 Office Action and requests that substantive examiniation be taken.

B. Status of the Specification

The specification has been amended at the suggestion of the Action. Sequence ID Nos have been added in the description in accordance with the enclosed Sequence Listing, and as requested by the Action. Further, the two references to an identity of 95% between the rat and human sequences has been corrected in the disclosure to correct an uncertainty that this percentage of identity is at the nucleic acid level. Applicants submit herewith two blasts (Appendices 1 and 2) comparing the exon sequences between the rat SCN1A sequence and the human neo-natal SCN1A (SEQ ID NO:1; "sequence 1 from WO 0138564") and adult human SCN1A (SEQ ID NO:2; "sequence 2 from WO 0138564"). Both blasts gave an 89% identity. At the protein level, the identity is indeed higher than 95%. Based on the fact that the recitation "at the protein level" should have been present to avoid this uncertainty, that the sequences of the rat and human were known at the time of filing and that the alignments had been performed at

the time of filing, Applicants respectfully request that the Action agrees to the correction of this mistake, which is submitted not to add new matter.

C. Status of the Claims

Claims 7, 8, 10, and 14-30 were pending at the time of the Office Action dated December 22, 2003 was issued. Claims 7, 8, 10, 14, and 20-30 have been amended and claims 31-41 have been added. Support for the amendments and newly added claims can be found throughout the specification and claims as originally filed. No new matter has been entered by the amendments. *See, e.g.*, the specification, pages 37 to 50; page 52, Example 3; and at page 57, Example 7.

Additional non-limiting support relating to voltage-gated sodium channel activity in generation of action potential in nerve cells and muscle cells (*e.g.*, claims 7, 31, 33 and 39) can be found, for example, at page 3, lines 2-3. Additional non-limiting support concerning sodium channel deregulation in epilepsy in general and in conditions outside of epilepsy can be found, for example, at page, 1 lines 14-18; page 21, lines 12-21; page 36, line 29, to page 37, line 4; page 48 line 22; and page 49, lines 25-26. Additional non-limiting support for SCN1A ion channel activity in general can be found, for example, at page 19, line 20 to page 20, line 19; page 38, lines 18-20; page 40, lines 16-30; page 41, lines 1-14; and at page 50 lines 1-9. Additional non-limiting support regarding ion flux in channels (*e.g.*, claims 31, 33, 34, 35 and 37) can be found, for example, at page 38, line 2; page 48, line 4; and page 58 line 22.

Additional non-limiting support for the activity assayed (*e.g.*, claims 31-38) can be found, for example, as follows: Voltage dependence activation support can be found, for example, at page 19, lines 20-26; and page 48, lines 5-9. Additional support relating to voltage dependence of steady state level of inactivation can be found, for example, at page 19 lines 28-29; and at

page 20, line 1. Additional support concerning time course of inactivation can be found, for example, at page 20, line 1; at page 21, lines 20-21; and at page 48, lines 3-5. Additional support relating to the number or fraction of channels available for opening can be found, for example, at page 59, line 9. Additional support relating to the change of current can be found, for example, at page 38, line 25, to page 39, line 2. Additional support for phosphorylation of SCN1A channel can be found, for example, at page 20, line 15; and at page 45, lines 4-8. Support regarding SCN1A binding assays can be found, for example, at page 20, lines 9-13; page 38, lines 18-20; page 39, lines 5-26; and page 28, lines 13-17. Additional support concerning induction of a second cellular messenger can be found, for example, at page 41, lines 3-14. Additional support for fluorescence resonance energy transfer (FRET)-based assays can be found, for example, at page 39, lines 29-30; page 40, lines 1-15; and page 47, lines 24-27. Support for assays using dibasic dyes can be found, for example, at page 38 lines 1-4. Additional support concerning radiolabeled guanidine assays can be found, for example, at page 38, line 3. Support for two electrode voltage clamp and patch clamp assays can be found, for example, at page 47, line 27. Further support for patch-clamp assays can be found, for example, in Example 7, from page 58, line 12, to page 59, line 15. Further support for sodium channel blockers, in claim 39, can be found, for example, at page 59, lines 19-24.

D. Sequence Listing

The Action objects to the Sequence Listings filed December 9, 2002 and September 22, 2003. The Action requests a clear listing of all the changes made in the Sequence Listing as well as an explanation of each sequence modification introduced in the substitute Sequence Listing filed on September 22, 2003. The Action alleges that the revised Sequence Listing introduces new matter into the disclosure.

Applicants traverse. No new matter has been added to the specification. Only clerical errors (*e.g.* in the name of the inventors) or errors in the Sequence Listing format were corrected in all the Sequence Listings previously filed. No new subject matter was, therefore, introduced in the specification. In order to clarify the record, Applicants provide the following explanation of the corrections made to the sequence listing.

1. The first Sequence Listing was filed on December 4, 2001 following a Notice to Comply with Requirements for Patent applications containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures dated June 4, 2001.

2. A second Sequence Listing was submitted on February 21, 2002 in response to a Notice of Incomplete Reply dated January 7, 2002. The following corrections were requested by the USPTO:

(a) Correct the spelling of the inventor's name-correction of accent mark in Lafrenière.

(b) Correct the content of field 140 and 150 (corresponding to the current application number and the earlier application number respectively) in the Sequence Listing.-- In the Sequence Listing dated December 4, 2001, the content of fields 140 and 150 were inverted.

(c) Correct title. Delete duplicate "or'' in the title (two "or'' were mistakenly introduced in the title).

(d) Define and identify/locate the n's and Xaa's in SEQ ID NOs: 4, 23, 41, 42, 44, 48, 55, 67, 68, and 84.

Unfortunately, the original Sequence Listing filed on December 4, 2001 was mistakenly resubmitted instead of the corrected Sequence Listing.

3. A third Sequence Listing was submitted on June 7, 2002 in response to a Notice to Comply with requirements for Patent applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures dated April 9, 2002. In this Sequence Listing, corrections corresponding to points 2(a) to 2(d) above were made. However, the positions as well as the

definitions of n's and Xaa's in SEQ ID NOs 4, 23, 41, 42, 44, 48, 55, 67, 68, and 84 were improperly defined.

4. A fourth Sequence Listing was prepared and submitted on December 4, 2002. SEQ ID NO: 4 was previously improperly labeled as a DNA sequence so that the one letter amino acids were interpreted as nucleotides. Therefore, a Sequence Listing comprising the correctly labeled SEQ ID NO: 4 was submitted. This was supposed to be the only modification introduced in the Sequence Listing (Sequence Listing number 3). However, it was mistakenly prepared by using the original Sequence Listing filed on December 4, 2001 and February 21, 2002 and therefore contained all the previously identified errors (see points 1, 2 and 3 above), except that SEQ ID NO:4 was now defined as a protein sequence instead of a DNA sequence.

5. Finally, a fifth Sequence Listing was filed on September 22, 2003 in response to an Office Action dated March 25, 2003. The Action noted in this Office Action that the previously submitted computer readable format (CRF) of the Sequence Listing could not be processed by the Scientific and Technical Information Center (STIC) and requested that another CRF be submitted. Since Sequence Listing no. 4 still contained errors that were already supposed to be corrected by the filing of the previous Sequence Listing (see point 4 above), another Sequence Listing was prepared.

As a result, a corrected Sequence Listing comprising all the requested modifications (corrected inventor's name, corrected fields, corrected title, proper definition/identification of n's and Xaa's in the sequences, and SEQ ID NO:4 defined as a protein sequence) was filed. However, while making the required changes yet another error slipped into the fifth Sequence Listing. In SEQ ID NO: 23, position 415 was described as being (415)...(451) instead of (415)...(415).

Consequently, a sixth Sequence Listing is now provided herewith along with the statement under 37 CFR 1.825(a) and (b). A petition under 37 CFR 1.48(a) was filed on April 30, 2004 for the correction of inventorship in the instant case. The requested change includes the addition of Patrick Cossette and David Ragsdale as inventors. Therefore the Sequence Listing provided herewith corrects the identification of position (415) in SEQ ID NO 23 (now defined as (415)...(415)) and include the names of the two inventors recently added (Patrick Cossette and David Ragsdale).

Applicants believe that everything relating thereto is in order.

E. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Are Overcome

The Action rejects claims 7, 8, 10 and 14-30 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Applicants traverse. The present claims satisfy all of the requirements of 35 U.S.C. § 112, second paragraph. Applicants address each indefiniteness rejection separately in the following subsections.

1. Claims 7 and 8 are Definite

The Action takes the position that claims 7 and 8 are indefinite because "it is unclear if the compound in line 2 and test agent, in line 9 is the same or different compound." The Action , page 4.

Applicants traverse. A person of ordinary skill in the art would be able to understand the scope of the term "agent" when read in light of the present invention. *See The Manual of Patent Examining Procedure* (MPEP) § 2173.02 (8th ed. inc. rev. 1, 2003) ("The test for definiteness under 35 U.S.C. § 112, second paragraph is whether those skilled in the art would understand what is claimed when read in light of the specification.") (citations and internal quotations

omitted); *see also Miles Lab., Inc. v. Shandon Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993) ("If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, [section] 112 demands no more"). The specification, in fact, defines "agent" and states that this term can be used interchangeable with the term "compound." *See* the specification, page 20, lines 20-23. To further the prosecution of this case, however, claims 7 and 8 have been amended and now refer to a "test compound" rather than a "test agent." The rejection of claims 7 and 8 should therefore be withdrawn.

2. Claim 10 is Definite

The Action contends that the phrase "providing a screening assay which comprises a measurable SCN1A biological activity," as that phrase is used in claim 10, is unclear. Specifically, the Action states that "it is unclear how a screening assay can comprise an activity."

Applicants traverse. The phrase "providing a screening assay which comprises a measurable SCN1A biological activity" is definite when read in light of the present specification. *See* the MPEP § 2173.02. In an effort to further the prosecution in this case, claim 10 now recites: "providing a screening assay which assesses a measurable SCN1A biological activity." Present claim 10 is definite. *Id.* The rejection of claim 10 should therefore be withdrawn.

3. Claims 14, 17, 19-21, and 23 are Definite

The Action contends that claims 14, 17, 19-21, and 23 are indefinite because they "appear to further define products and not methods."

Applicants traverse. This rejection is improper because method claims can be further defined by the product that is used in the method. Applicants request that the Action provide a legal basis to support this rejection if the rejection is maintained in a future office action. In effort to further the prosecution, however, claim 14 now refers to an assay "wherein said SCN1A

biological activity in step a) is provided by and expression vector." A person of ordinary skill in the art would understand the scope of this claim when read in light of the present specification. *See* MPEP § 2173.02. Because claims 20, 21, and 23 depend from claim 14, the rejection of these claims are rendered moot. The rejection of claims 10, 14, 17, 19-21, and 23 should therefore be withdrawn.

F. The New Matter Rejection Is Overcome

The Action rejects claims 20, 21, and 22 under 35 U.S.C. § 112, first paragraph, for lack of written description. It is alleged by the Action that these claims contain new subject matter because the claims recite SEQ ID NOs which have been changed in the substitute Sequence Listing. As requested by the Action, Applicants have provided an explanation that fully supports the substitute sequence listing submitted with this document. It is apparent by the explanation given above that no new matter is present in claims 20, 21, and 22.[1]

The new matter rejection of claims 20, 21, and 22 should therefore be withdrawn.

G. The Enablement Rejections Are Overcome

1. A Summary of the Rejection

The Action rejects claims 7, 8, 10, and 14-30 under 35 U.S.C. § 112, first paragraph, for lack of enablement. It appears that the Action contends that the application does not support an assay/method for selecting compounds that affect SCN1A activity that have a therapeutic effect on any type of epilepsy or any neurological disorder. The Action admits, however, that the specification has established an association between certain mutations in human SCN1A sodium channel and idiopathic generalized epilepsy. According to the Action, there is no teaching in the

[1] Applicants note that SEQ ID NO: 23 contained n's in all of the Sequence Listing filed with the U.S. Patent Office. The first, second, and fourth Sequence Listing submitted, however, did not define or identify properly these nucleotides.

specification that a predictable correlation can be made that modulation of SCN1A would be therapeutic in different types of epilepsies.

Applicants traverse. Claims 7, 8, 10, and 14-30 are enabled by the specification and satisfy all of the requirements of 35 U.S.C. § 112, first paragraph.

2. The Standard for Enablement

It is well-settled that "the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." MPEP § 2164.04. The standard for enablement has been stated by the Federal Circuit as:

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation.

United States v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1988); *see also* MPEP § 2164.01.

It has been settled that enablement must bear only a ***reasonable*** relationship to the scope of the claims. *See In re Fisher*, 166 U.S.P.Q. 18, 24 (CCPA 1970). Moreover, the Federal Circuit has held that "[t]he enablement requirement is met if the description enables ***any*** mode of making and using the invention." *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998) (emphasis added) (quoting *Engel Indus. Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991)) (emphasis added). This is confirmed by the MPEP which states: "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP 2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970)). Furthermore, "[a] patent applicant is not required . . . to predict every possible variation, improvement or commercial embodiment of his invention." *United States Steel Corp. v. Phillips Petroleum Co.*, 673 F. Supp. 1278, 1292 (D.

Del. 1987), *aff'd,* 865 F.2d 1247, 1250 (Fed. Cir. 1989) (specifically quoting this statement). In the end, all that is required for enablement is objective enablement, not any particular level of efficacy. *In re Marzocchi*, 169 UPSQ 370 (CCPA 1971).

3. The Present Claims Are Enabled By the Specification

i. The specification teaches how to make the claimed invention.

A person of skill in the art could make the presently claimed invention from the disclosure in the specification alone or in combination with information known in the art without undue experimentation. By way of example only, the specification identifies numerous cell-based and cell-free assays that can be used to screen test compounds. *See, e.g.*, the specification, page 37, line 12, to page 47, line 20. The specification also provides non-limiting examples of how to obtain an SCN1A nucleic acid and how to express the nucleic acid (*e.g.*, expression vectors). *See, e.g.*, the specification, page 17, lines 3-25; *see also* the provided sequence listings. Also provided by the specification is non-limiting examples of how to obtain test compounds. *See, e.g.*, the specification, page 48, line 25, to page 49, line 22.

It is clear from the specification that a person of reasonable skill in the art can make the presently claimed invention without undue experimentation. The Action, in fact, does not appear to contend otherwise. Rather, it appears that the Action is taking the position that undue experimentation is required to use the invention for identifying compounds that can be used to treat or prevent "any type epilepsy or any neurological disorder." *See* the Action, page 10.

ii. The specification teaches how to use the claimed invention.

The specification teaches a person of reasonable skill in the art how to use the present invention for any type of epilepsy or any neurological disorder. The Action, in fact, admits that "[t]he specification has established an association between certain mutations in human SCN1A

sodium channel and idiopathic generalized epilepsy." The Action, page 7. This and other data disclosed in the specification provides "a reasonable correlation" to the scope of the present claims. *See, e.g.*, the specification, Examples 3-6. That is all that is required to establish enablement. *See, e.g.*, MPEP 2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970)) ("As long as the specification discloses at least ***one method for making and using the claimed invention*** that bears a reasonable correlation to the entire scope of the claim, ***then the enablement requirement of 35 U.S.C. 112 is satisfied***." (emphasis added)). The following provides a more detailed explanation of Applicants' position.

To begin, many known sodium channel blocker drugs are used routinely for several indications outside of epilepsy. Examples include anti-convulsants generally, analgesia (pain), anti-arrhythmias, and euphorics. Drugs that have these effects have been known and available for years. Specific examples include cocaine, phenytoin, carbamazepine, lidocaine, and lamotrigine. Lamotrigine, for example, was found useful not only in the treatment of epilepsy but also in the treatment of bipolar disorders. Carbamazepine may be prescribed as an anticonvulsant or in the treatment of acute mania and was also found useful in the prophylactic treatment of bipolar disorders. Phenytoin has anticonvulsant and antiarrythmic activities. It is well known in the art that there are many uses for sodium channel modulating compounds. The instant claims recite compounds having a therapeutic effect on epilepsy and other neurological disorders associated with an abnormal activity of a voltage gated sodium channel.

Second, as part of the great voltage-gated SCNA sodium channel family, SCN1A plays a role in the general regulation of action potential in nerve cells and muscles. By demonstrating its importance in idiopathic generalized epilepsy and generalized epilepsy with febrile seizures, Applicants have highlighted the biological importance of SCN1A in the regulation of action

potential in cells. *See, e.g.*, the specification, page 52, lines 1-27 (Example 3); page 54, line 17, to page 57, line 7 (Example 6). Because SCN1A is implicated in the regulation of action potential in cells, it follows that SCN1A modulating compounds find usefulness in the treatment of many conditions associated with an abnormal activity of a voltage gated sodium channel activity, outside of epilepsy.

Third, epilepsy is a recurrent seizure disorder caused by abnormal electrical discharges from brain cells. Normal nerve transmission in the brain occurs in an orderly way allowing a smooth flow of electrical activity. A seizure occurs when neurons generate uncoordinated electrical discharges that spread through the brain. Applicants have demonstrated that specific mutations in SCN1A are directly involved in 2 types of epilepsy (IGE and GEFS). *Id.* Although epilepsy may be triggered by many causes, several types of epilepsy or other neurological disorders associated with an abnormal sodium channel activity are predicted to benefit from compounds which regulate the ion channel activity of SCN1A which is shown to be implicated in the general regulation of action potential in neural cells and therefore contribute to the regulation of nerve transmission.

In view of the data presented in Applicants' specification and the general knowledge in the field of sodium channels, Applicants submit that the present claims are enabled for identifying a compound useful in any type of epilepsy and neurological disorder that is associated with abnormal voltage-gated sodium channel activity. *See United States Steel Corp. v. Phillips Petroleum Co.*, 673 F. Supp. at 1292 ("A patent applicant is ***not required*** . . . to predict every possible variation, improvement or commercial embodiment of his invention") (emphasis added). In the end, all that is required for enablement is objective enablement, not any

particular level of efficacy. *See In re Marzocchi*, 169 UPSQ 370 (CCPA 1971). Applicants' specification does this and, therefore, enables the present claims.

iii. The remaining enablement rejections are overcome

a. The term "allelic variant" is enabled by the specification.

The Action appears to reject claims 7, 8, 10, and 14-30 as being too broad as including administering a compound to a SCN1A sodium channel from any source, or any mammalian source, or any functional fragments thereof, including allelic variants and genomic sequences not described in the application.

Applicants traverse. Claims 7, 8, 10, and 14-30 are fully enabled by the present specification.

Applicants note that the claims now refer to <u>human</u> SCN1A sodium channels. Claims 7, 8, 14, and 22 also no longer recite "functional fragment" or "fragment." Regarding the phrase "allelic variant" in claims 20 and 21, the specification states:

> This invention now establishes, for the first time, that SCN1A, SCN2A, and SCN3A, is directly responsible for idiopathic generalized epilepsy (IGE) in certain human populations. Further, this discovery suggests that compounds which modulate the activity of SCN1A, SCN2A and SCN3A may have application far beyond the small groups of families with IGE, and may have applicability for treating many or all forms of epilepsy and related neurological disorders. It is therefore an object of this invention to provide screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders.

The specification, page 36, line 27, to page 37, line 11. The specification validates that specific mutations in SCN1A (*see, e.g.,* Examples 3 and 6) affect the function of the sodium channel. Applicants have identified a number of mutations in sodium channels associated with epilepsy (*e.g.*, Glu1238Asp, Ser1773Tyr and Asp188Val) in SCN1A. Applicants, therefore, are the first to validate that SCN1A is directly involved in epilepsy. The specification also shows how to assess the structure-function relationship of the sodium channels of the present invention, and

therefore, other mutations can be identified and tested as explained, for example, in Examples 6 and 7. Applicants' specification provides a "reasonable correlation" to the entire scope of the present claims. Therefore, the specification fully enables allelic variants of SCN1A and the rejection should be withdrawn. *See* MPEP 2164.01(b).

b. The scope of the present claims are enabled by the specification.

The Action also alleges that "[t]he specification provides no working examples of any compounds that were screened for SCN1A, nor any actual screening methods undertaken for selecting any compounds that have any effect on any SCN1A biological activity or any modulation of inactivation of sodium channel or any modulation of sodium channel activity." The Action, page 8. According to the Action, the specification provides no guidance as to critical amino acid residues required for SCN1A channel activity. The Action also apparently contends that the recitation of "biological activity of SCN1A" is too broad as it encompasses any activity of the channel whatsoever. The Action also alleges that the specification provides no working example of screening assays or compounds that affect SCN1A activity that have a therapeutic effect on any type of epilepsy or any neurological disorder. In conclusion the Action states that the claims encompass an extremely large amount of experimentation requiring extensive trial and error analysis, the result of which is alleged to be unpredictable.

Applicants traverse. The present claims are fully enabled by the specification.

It is well-settled that enablement does ***not*** require an applicant to actually reduce the invention to practice prior to filing. *See* MPEP § 2164.01(c). Further, the specification "***need not*** contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *Id.* The Federal Circuit has stated that the satisfaction of the enablement requirement is not precluded by

the necessity of some experimentation. *See Atlas Powder Co. v. E.I. duPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409 (Fed. Cir. 1984).

In the present case, it is undisputed that Applicants' specification includes a number of non-limiting examples of screening assays for assessing numerous SCN1A sodium channel activities. *See, e.g..*, the specification, page 37, line 12, to page 50, line 20. Examples of non-limiting assays disclosed in the specification include:

- Direct measure of flux of sodium or related ions in a cell line by fluorescence based assays using both sodium indicator dyes and voltage sensitive dyes (e.g. ^{14}C guanidine flux, SBFI, DIBAC and $DIBAC_4$). Page 37 lines 23 to page 38, lines 1 to 6.
- Indirect evaluation of SCN1A sodium channel activity in cells by assessing the release of a neurotransmitter or other compound which is affected by the activity of SCN1A. Page 38, lines 14 to 28.
- Assessment of SCN1A sodium channel activity by current measurement using patch-clamp techniques. Page 38, line 29 to page 39, line 4 and Example 7.
- Functional assay using the Xenopus oocyte model and voltage clamp electrophysiological recording. Example 7, from page 58 line 3 to 59 line 15.
- Binding assays using radiolabeled, enzymaticaly-labeled or fluorescently-labeled substrate. Page 39, lines 5 to 16.
- Binding assays using microphysiometer. Page 39, lines 17 to 27.
- Assessment of changes in membrane potential induced by SCN1A activity using the voltage ion probe reader VIPR™ (voltage sensitive FRET mechanism). From page 39, line 29 to page 40, line 15.
- Assays to identify compounds which indirectly modulate SCN1A activity by targeting the activity of a SCN1A interacting partner. Page 40 lines 16 to 30.
- Assays which indirectly evaluate SCN1A sodium channel activity by measuring a secondary activity modulated by SCN1A (e.g. measurement of enzymatic activity or induction of cellular second messenger- intracellular Ca^{2+}, diacylglycerol, IP3 etc.). From page 30, line 30 to page 40, line 14.

These assays can be used to evaluate directly or indirectly an SCN1A biological activity. Such assays are well known and routinely used by people of ordinary skill in the art. An example includes the teachings of Gonzales *et al.* (1999), which is cited in the specification. The specification, page 37, lines 25-27. This reference contains information relating to standard ion

channel assays—assays that were known when Applicants identified the SCN1A gene/protein of the present invention. Because a person of ordinary skill in the art would be able to practice such assays without undue experimentation, it follows that such a person would be able to incorporate the specific teachings disclosed in Applicants' specification to screen test compounds. This is supported by the MPEP which states: "[t]he specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." The present claims, therefore, are enabled by the specification.

c. The phrase "SCN1A biological activity" is enabled.

The specification also enables the use of the phrase "SCN1A biological activity" in the claims. Several screening assays for numerous types of SCN1A biological activities are described in the specification and can be used without undue experimentation. *See* above. Moreover, the specification defines and explains this phrase. *See* the specification, page 19, line 20, to page 20, line 19. The definition, in fact, includes activities that are standard and routine in the art. The MPEP confirms that this phrase is enabled by the specification: "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP 2164.01(b). The phrase "SCN1A biological activity" is therefore enabled by the specification.

d. The identification of test compounds is enabled.

The present invention also enables a person skilled in the art to identify compounds that modulates SCN1A sodium channel activity without undue experimentation. The specification describes a novel drug target *i.e.*, a sodium channel with great physiological importance in

humans for use in screening assays. Ion channel analysis is routinely performed commercially by several major drug company, and thousands of academic laboratories. Hundreds of different types of libraries of compounds are commercially available and could be used for screening for compounds which modulate a sodium channel activity of SCN1A. These libraries are regularly used in screening assays for several types of potential targets. As described in a non-limiting way in the specification, the test compounds to be used in the screening assays of the present invention can be obtained using any of the numerous approaches in combinatorial library methods well known in the art. *See* the specification, page 48, line 23, to page 49, line 22. Based on the specification and on the general state of the art, Applicants submit that a person skilled in the art would know how to identify compounds which modulates SCN1A sodium channel activity without undue experimentation.

Applicants also note that the claims are drawn to screening assays to identify modulators of SCN1A activity and not to the compounds themselves nor to methods of treating epilepsy or other neurological disorders. Limiting the claims to a particular disorder (*e.g.* idiopathic generalized epilepsy) would unfairly restrict the scope of the claims. The specification and the knowledge of those skilled in the art enable the present claims to any epilepsy and any neurological disorder. *See* above.

e. The identification of specific amino acid residues is not required.

The Action also contends that the identification of critical amino acids residues required for SCN1A biological activity is necessary in order to perform an assay for identifying SCN1A modulating compounds. It is also contended by the Action that the specification does not provide any guidance as to those critical residues.

Applicants take the position that the identification of specific amino acids is unnecessary. It is noted however, that such critical amino acids are identified in the specification. Applicants were the first to provide the SCN1A gene, its protein sequence, allelic variants of SCN1A and a validation of SCN1A as a gene involved in a neurologic disorder. The combination of the sequence information, the validation, and the assays provided by the present invention which describe how to measure or evaluate SCN1A activity are useful to identify compounds and residues that modulate SCN1A activity. As discussed throughout this document, such assays are well described in the specification. Applicants further note that by having identified specific mutations in SCN1A and by demonstrating that such mutations can affect the sodium channel activity of SCN1A (see Example 7), critical residues have in fact been identified. Moreover, the residues which are shown to be critical for SCN1A normal ion channel activity identify residues that may be critical in other known sodium channels.

In summary, Applicants have identified SCN1A as a drug target. The screening assays are described in the specification along with the libraries of compounds that can be used. A person skilled in the art would be able to screen and identify compounds useful for treating epilepsy or other neurological disorders associated with deregulation of sodium channel activity without undue experimentation.

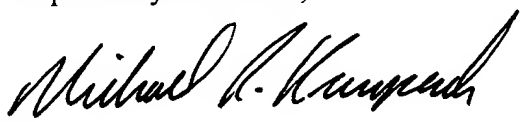
Accordingly, Applicants request that the rejection of claims 7, 8, 10, and 14-30 under 35 U.S.C. § 112, first paragraph, for lack of enablement be withdrawn.

H. Conclusions

Applicants believe that the present document is a full and complete response to the Office Action dated September 1, 2004. The present case is in condition for allowance, and such favorable action is respectfully requested.

It is believed that no fee is due for filing this Response to the Office Action dated September 1, 2004. However, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to this document, consider this paragraph such a request and authorization to withdraw the appropriate fee from Fulbright & Jaworski Deposit Account No. 50-1212/GOUD:023US.

Respectfully submitted,



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